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(54) Title: LIQUID ORAL PHARMACEUTICAL COMPOSITIONS HAVING ANTI-INFLAMMATORY ACTIVITY

(57) Abstract

Liquid pharmaceutical compositions for the oral topical treatment, containing as the active ingredients non steroidal anti-inflammatory drugs, characterized in that they contain dimethyl isosorbide as the carrier.

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It is under examination in which parts of the former Soviet Union the designation of the Soviet Union has effect.

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LIQUID ORAL PHARMACEUTICAL COMPOSITIONS HAVING ANTI-INFLAMMATORY ACTIVITY

The present invention relates to liquid pharmaceutical compositions for the oral topical treatment, containing non steroidal anti-inflammatory drugs as the active ingredients.

Therapeutical treatment of inflammations of the oral cavity, such as aspecific odontostomatologic affections, gingivitis, glossitis, stomatitis and the like, is particularly complex and, until the specific pathogenic agent has precisely been determined, treatment can be restricted to the use of disinfectants of the general type.

Moreover, even when the pathogenic agent has certainly been determined, administration of antibiotics such as tetracyclines and the like, generally by the parenteral or systemic routes, must be carried out in most cases.

Said drugs, besides showing negative characteristics (remarkable side-effects) can cause severe and diffused allergy phenomena, so as to compel to immediately interrupt treatment and to take suitable restoration measures.

Now it has been found, and it is the object of the present invention, that pharmaceutical compositions comprising non steroidal anti-inflammatory drugs (FANS) in form of solutions intended for the oral topical treatment (collutories), allow to obtain very good therapeutical results without causing sensitization phenomena.

The compositions of the invention are characterized by the presence of a specific excipient, dimethyl isosorbide, giving them advantageous antiseptic properties together with an antiplaque action which is particularly desired in this kind of preparations. Anti-inflammatory properties of the active ingredients also turn out to be surprisingly enhanced through a synergetic interaction with dimethyl isosorbide.

The compositions of the present invention can contain the active ingredient in amounts ranging from 0.001 to 20% by weight, whereas dimethyl isosorbide can be present in amounts ranging from 1 to 40% by weight.

Of course, the compositions of the invention can also contain other excipients and/or coadjuvants, such as surfactants, flavouring and sweetening agents, in order to give the preparation suitable organoleptic characteristics. Examples of said excipients and/or coadjuvants conventionally used for the preparation of collutories are described in "Remington's Pharm. Sciences Handbook", Mack Pub. Co., NY. The compositions of the invention will preferably contain natural and/or synthetic sweetening agents such as saccharine, ammonium glycyrrhizinate, cyclamate or, more preferably, not cariogenic carbohydrates such as xylitol and sorbitol.

All the up to now known non steroidal anti-inflammatory drugs such as ketoprofen, ibuprofen, ibuprofen lysine salt, naproxen, suprofen, diclofenac, alclofenac, indomethacin, acemethacin, benzidamine, flurbiprofen, piroxicam and the like, can be used as active ingredients, either in the free form or salified, in

order to improve the solubility thereof.

According to a particularly preferred embodiment, the active ingredients are present in combination with cyclodextrins or derivatives thereof, for example in form of physical admixtures, inclusion products or co-precipitates. Cyclodextrins or derivatives thereof, such as hydroxypropyl beta-cyclodextrins, involve favourable pharmacokinetic effects and, moreover, are useful to increase solubility and stability, or to improve the organoleptic characteristics of the medicament.

Cyclodextrin contents can range from 0.5 to 50% by weight of the finished composition, but equimolecular ratios of active ingredient to cyclodextrin are preferably used. Besides the commonly available cyclodextrins (α, ß, γ) and the already cited hydroxypropyl ß-cyclodextrin, dimethylcyclodextrins or other derivatives, possibly in a mixture thereof, can also be used.

The techniques for the preparation of both inclusion complexes with cyclodextrins and co-precipitates are well-known. In principle, the active ingredient is added to an aqueous solution of cyclodextrin or hydroxypropyl ß-cyclodextrin, keeping the mixture under stirring for 40-80 hours at a temperature from the room one to 80°C. The desired compound is obtained upon evaporation of the solvent under vacuum.

Another particularly preferred embodiment of the invention is provided by formulations in which polymers having an adhesive power towards mucosae are used as excipients. Examples of said polymers are provided by carboxyvinyl polymers, ethylene oxide - propylene oxide

copolymers, cellulose derivatives such as carboxymethyl cellulose, calcium carboxymethyl cellulose, hydroxypropylethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carrageenan, dextrins, natural or synthetic gums and the like. Said excipients, which can be defined bioadhesive polymers, can be present in percentages ranging from 0.5 to 30%, preferably from 1 to 5%. The use of said excipients allows to obtain slightly viscous solutions having adhesiveness towards mucosae, so as to achieve a better persistence of the preparation in contact with the area to be treated, thus obtaining a more effective and lasting action.

Whenever said bioadhesive polymers are present, the compositions can also contain no dimethyl isosorbide : said compositions also fall within the scope of the present invention.

The following examples further illustrate the invention.

EXAMPLE 1

Collutory containing ketoprofen (in form of solution)

100 ml of collutory contain (% composition)

Active ingredient:

ketoprofen	0.0133 to 0.133

Excipients:

Tween 60	0.5
alpine herb flavor 52,503 T	0.100
dimethyl isosorbide	10
90% ethanol	15
sodium saccharinate	0.1
Sodium benzoate	0.2
70% sorbitol solution	10

distilled water q.s. to ml	100

Each 15 ml ampoule contains:

Active ingredient:

ketoprofen	2 to 20 mg

Excipients:

Tween 60	5 mg
alpine herb flavor 52,503 T	15 mg
dimethyl isosorbide	1500 mg
90% ethanol	2250 mg
sodium saccharinate	15 mg
Sodium benzoate	30 mg
70% sorbitol solution	1500 mg
distilled water q.s. to ml	100

Ketoprofen is dissolved in an ethanol solution containing dimethyl isosorbide and Tween 60, the solution is heated to 35°C under stirring, to obtain a clear solution which is added with the other components. After filtration, a clear homogeneous solution (collutory) is obtained.

EXAMPLE 2

Collutory containing ketoprofen - ß-cyclodextrins (solution)

100 ml of collutory contain (% composition):

Active ingredient:

ketoprofen	0,25

Excipients:

ß-cyclodextrin	1.14
dimethyl isosorbie	10.00
ethanol	15.0
sodium saccharinate	0.1
sodium benzoate	0.2

70% sorbitol solution	10.0
distilled water q.s. to ml	100

Ketoprofen is added to a ß-cyclodextrin aqueous solution (about 50 ml), which is heated to 30-40°C for 30 hours. A solution is obtained which is added with dimethyl isosorbide and the other components, then filtered.

EXAMPLE 3

Collutory containing ketoprofen and bioadhesive polymers (solution)

100 ml of collutory contain (% composition):

Active ingredient:

ketoprofen	0.05

Excipients:

Ethylene oxide-propylene oxide copolymer (Poloxamer 188)	1.2
ethanol 95°	5.0
sodium benzoate	0.1
sodium saccharinate	0.3
benzoic acid	0.05
natural flavor	0.05
depurated water q.s. to ml	100

EXAMPLE 4

Collutory containing ketoprofen, dimethyl isosorbide and bioadhesive polymers (in form of solution)

100 ml of collutory contain (% composition):

Active ingredient:

ketoprofen	0.05

Excipients:

Ethylene oxide-propylene

oxide copolymer	
(Poloxamer 188)	1.2
dimethyl isosorbide	5.0
ethanol 95	5.0
sodium benzoate	0.1
sodium saccharinate	0.3
benzoic acid	0.05
natural flavor	0.05
depurated water q.s. to ml	100

Ketoprofen is dissolved in ethanol, dimethyl isosorbide and Poloxamer 188 are added, then about 50 ml depurated water and the other components. The mixture is filtered to obtain a clear light solution.

EXAMPLE 5

Collutory containing benzidamine (in form of solution)

100 ml of collutory contain (% composition):

Active ingredient:

Benzidamine	0.0133 to 0,133

Excipients:

Tween 60	0.5
alpine herb flavor 52,503 T	0.100
dimethyl isosorbide	10
90% ethanol	15
sodium saccharinate	0.1
sodium benzoate	0.2
xylitol	10
distillated water q.s. to ml	100

Each 15 ml ampoule contains :

Active ingredient:

Benzidamine	2 to 20 mg

Excipients:

Tween 60	5 mg
alpine herb flavor 52,503 T	15 mg
dimethyl isosorbide	1500 mg
90% ethanol	2250 mg
sodium saccharinate	15 mg
sodium benzoate	30 mg
xyilitol	1500 mg
distillated water q.s. to ml	100

EXAMPLE 6

Collutory containing ibuprofen lysinate (in form of solution)

100 ml of collutory contain (% composition) :

Active ingredient:

Ibuprofen lisinate	0.0266 to 0,266

Excipients:

Tween 60	0.5
alpine herb flavor 52,503 T	0.100
dimethyl isosorbide	10
90% ethanol	15
sodium saccharinate	0.1
sodium benzoate	0.2
70% sorbitol solution	10
distillated water q.s. to ml	100

Each 15 ml ampoule contains :

Active ingredient:

Ibuprofen lisinate	4 to 40 mg

Excipients:

Tween 60	5 mg
alpine herb flavor 52,503 T	15 mg
dimethyl isosorbide	1500 mg
90% ethanol	2250 mg

sodium saccharinate	15 mg
sodium benzoate	30 mg
70% sorbitol solution	1500 mg
distillated water q.s. to ml	100

EXAMPLE 7

Collutory containing piroxicam (in form of solution)

100 ml of collutory contain (% composition):

Active ingredient:

Piroxicam	0.001 to 0,01%

Excipients:

Tween 60	0.5
alpine herb flavor 52,503 T	0.100
dimethyl isosorbide	10
90% ethanol	15
sodium saccharinate	0.1
sodium benzoate	0.2
70% sorbitol solution	10
distillated water q.s. to ml	100

Each 15 ml ampoule contains:

Active ingredient:

Piroxicam	1 to 10 mg

Excipients:

Tween 60	5 mg
alpine herb flavor 52,503 T	15 mg
dimethyl isosorbide	1500 mg
90% ethanol	2250 mg
sodium saccharinate	15 mg
sodium benzoate	30 mg
70% sorbitol solution	1500 mg
distillated water q.s. to ml	100

CLAIMS

1. Liquid pharmaceutical compositions for the oral topical treatment, containing as the active ingredients non steroidal anti-inflammatory drugs, characterized in that they contain dimethyl isosorbide as the carrier.

2. Compositions according to claim 1, wherein dimethyl isosorbide is present in percentages from 1 to 40% by weight.

3. Compositions according to claim 1 or 2, wherein the active ingredient is present in percentages from 0.001 to 20% by weight.

4. Compositions according to any one of the preceding claims, wherein the active ingredient is selected from ketoprofen, ibuprofen, ibuprofen lysinate, suprofen, flurbiprofen, naproxen, diclofenac, alclofenac, benzidamine, piroxicam, acemethacin, indomethacin.

5. Compositions according to claim 4, wherein the active ingredient is ketoprofen.

6. Compositions according to any one of the preceding claims, wherein the active ingredient is combined with cyclodextrins or derivatives thereof, in form of mixtures, inclusion complexes or co-precipitates.

7. Compositions according to claim 6, wherein combinations with α, β or γ cyclodextrins or hydroxypropyl β-cyclodextrins are used in almost equimolecular ratios to the active ingredient.

8. Compositions according to any one of the preceding claims, further containing bioadhesive polymers.

9. Liquid pharmaceutical compositions for the oral topical treatment, containing as the active ingredients

non steroidal anti-inflammatory drugs, characterized in that they contain a bioadhesive polymer as an excipient.

10. Compositions according to claim 9, wherein the bioadhesive polymer is selected from carboxyvinyl polymers, ethylene oxide - propylene oxide copolymers, cellulose derivatives, carrageenan, dextrins, natural or synthetic gums.

INTERNATIONAL SEARCH REPORT

International Application N[redacted] PCT/EP 91/01245

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/00 A 61 K 47/26 A 61 K 47/32
A 61 K 47/36 A 61 K 47/38 A 61 K 47/40 A 61 K 47/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0284588 (PHARLYSE) 28 September 1988, see the claims; page 2, lines 46-59; page 3, example I	1-4
X	WO,A,8904179 (ALSO LABORATORI) 18 May 1989, see the claims; page 4, lines 29-30; page 5, lines 1,5-9	1,3,4,8-10
X	EP,A,0215423 (DOLORGIET) 25 March 1987, see the claims 1,5,10; column 10, examples 16,17; column 11, examples 18,19; column 12, example 20	1-5,8-10

* Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05-09-1991	04. 10. 91
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101245 SA 48898

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0284588.	28-09-88	BE-A- 1000381	16-11-88
		US-A- 5036100	30-07-91
WO-A- 8904179	18-05-89	AU-A- 2617288	01-06-89
EP-A- 0215423	25-03-87	DE-A- 3532562	12-03-87
		CA-A- 1269328	22-05-90
		JP-A- 62061917	18-03-87
		US-A- 4849418	18-07-89